being cleaved by the enzyme moiety of the bispecific reagent from the insoluble moiety, the solubilizing effect of the soluble moiety being thereby reduced and the remaining material being available to form the extra-cellular precipitate.

68 83. (amended) A therapeutic agent in accordance with claim 69 which is radio-labeled.

REMARKS

Claims 70, 73, 74, 76, and 81-83, the remaining claims under consideration have been set forth above to show amendments to claims 69, 71, 72, and 77-79 of the Amendment filed on November 29, 2000 as well as claims 70, 73, 74, 76, and 81-83 which remain under consideration.

In Paragraph 13 of the Action mailed on February 13, 2001, the Examiner incorrectly refused to enter the Amendment to claims 69, 71, 72, 75, and 77-79, filed on November 29, 2000, on the basis that the "submitted amendment is improper", citing the requirements of 37 CFR 1.121(b), and making reference to amended claim 77. First of all, 37 CFR 1.121(b) is limited to reissue applications. Claim 77 was amended properly in accordance with 37 CFR 1.121 (a), with the entire text of the claim taken with brackets showing deletions.

The Examiner evidently intended to object to the amendments to claims 69, 71, and 72. These claims were properly amended in accordance with 37 CFR 1.121(a) (2) (A) and (B).

In paragraph 5 on page 3 of the Action, the Examiner has objected "that the first line of paragraph 2 of page 4 of the Mayers' Declaration is illegible." A complete and legible copy of the Mayers' Declaration, dated November 27, 2000, is enclosed herewith.

RESPONSES TO CLAIM REJECTIONS IN SECTION 5 OF PAPER NO. 33, UNDER 35 USC SECTION 112 FIRST PARAGRAPH, BASED UPON PAPER NO. 10, SECTION 5, PAGES 2-5 OF ACTION

1. Action - Section 5.(a):

> "(a) The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a first therapeutic agent being a soluble precipitable material which is adapted to be converted into an insoluble and non-digestible precipitate by the action of a non-mammalian enzyme wherein the first therapeutic agent is selected from the group consisting of peptides, including opio-melanins, or carbohydrates including cellulose, chitosan and chitin, of proteglycans of synthetic polymers and of indoxyl compounds."

Response:

The making of soluble precipitable material is disclosed in the specification at pages 20-23 and the making of soluble precipitable material comprised of soluble and insoluble moieties is disclosed in the specification, at pages 23 and 24.

2. Action - Section 5.(a):

The specification contemplates the use of the therapeutic agent *in vivo* in the treatment of cancer (see page 2, paragraph 1 of the specification). However, the specification does not provide teachings to establish effective dosages or methods of administration of any of the claimed "adapted" moieties...".

Response:

The effective dosage and the methods of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-Drug Therapy" ("ADEPT") on pages 9 and 10 of the specifications.

3. Action - Section 5. (a):

> "...this specification does not providing teaching to... provide any guidance or exemplification on how to "adapt" any of the claimed moieties..."

Response:

The soluble precipitable material is deliberately made so that it is soluble and will precipitate by the action of an enzyme as set forth on pages 20-24 of this specification is the same as the prior art to the extent that, in ADEPT, the enzyme converts a molecule from one form into another form, but this conversion in ADEPT is that of converting a soluble pro-drug into a soluble drug. In contradistinction, in the present invention, the enzyme converts a chemical from one form to another, i.e. converts a soluble molecule into an insoluble molecule.

4. Action - Section 5.(a):

> "...for any of the limitations disclosed above or provide pharmacokinetic data that would provide guidance to one of skill in the art to predict the efficacy of the claimed therapeutic agent with a reasonable expectation of success..."

Response:

The effective dosage and the method of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-Drug Therapy" ("ADEPT") on pages 9 and 10 of the specification.

5. Action - Section 5.(a):

> "Clearly, the therapeutic agents may be inactivated *in vivo* before producing a therapeutic effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life. In addition, the therapeutic agent may not otherwise reach the target because it may be absorbed by fluids, cells and tissues where the therapeutic agent has no effect, circulation into the target area may be insufficient to carry the therapeutic agent and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled inthe art and no evidence has been provided which would allow one of skill int he art to predict the efficacy of the claimed therapeutic agent with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success."

Response:

The bispecific reagent is pharmacologically inactive. It has only two functions. It can bind to the platform and it has a non-mammalian enzyme moiety which can only act on the soluble precipitable material to convert it into an insoluble material. It is irrelevant if some is degraded, if some activates an immune response, if only a small fraction reaches the target platform, and if only a small concentration is achieved. That which does reach the platform remains bound and the amount which binds continues to increase until the binding sites on the platform are saturated. The binding of the bispecific reagent is directly analogous to the binding of a bispecific reagent to cell receptors as in ADEPT which is described in pages 9 and 10 of the specification. Since the enzyme in ADEPT can convert a pro-drug into an active drug and since the soluble precipitable material has been specifically made to be soluble and convertible to an insoluble material which remains near where it was made, the claimed therapeutic efficacy will be much better than the efficacy of ADEPT where the active drug diffuses away from its site of production to reach and cause systemic toxicity (see page 24 of the specification). The reasons why ADEPT fails is described on page 10 of the specifications.

6. Action - Section 5.(a):

> "Further, the specification provides no description of how to "adapt" any of the moieties so that they will be converted into an insoluble and non-digestible precipitate by the action of a non-mammalian enzyme. Applicant has not shown that, for example, peptides which are "adapted" are capable of functioning as that which is being disclosed. It is pointed out hat the term "adapted" could be read to encompass a variety of definitions, i.e. chemical modification, deletions, truncations, substitutions, conjugation, etc. Applicant has not enabled all of these types of modified peptides.

Response:

The word "adapted" has been replaced in claims 69, 74, 75, 76, and 84.

The effective dosage and the methods of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-drug Therapy" ("ADEPT") on pages 9 and 10 of the specification.

The soluble precipitable material is deliberately made so that it is soluble and will precipitate by the action of an enzyme as set forth on pages 20-24 of the specification is the same as the prior art described as ADEPT on pages 9 and 10 of the specification.

7. **Action - Section 5.(a):**

> Protein chemistry, which reads on peptide chemistry, is probably one of the most unpredictable areas of biotechnology. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein.

Response:

The Action is referring to the soluble precipitable material as being a protein or peptide. Proteins are <u>not</u> being claimed and the specification does <u>not</u> describe proteins and peptides as candidates for the soluble precipitable material.

8. **Action - Section 5.(a):**

> "Further, Applicant has not enabled "adaptations" of all carbohydrates, proteoglycans, synthetic polymers or indoxyl compounds as claimed. Nor has Applicant given guidance on how to choose those agents that will, upon "adaptation", function as claimed."

Response:

The making of soluble precipitable material is disclosed in the specification at pages 20-23 and the making of soluble precipitable material comprised of soluble and insoluble moieties is disclosed in the specification at pages 23 and 24.

9. **Action - Section 5.(a):**

> Finally it is not clear from the teaching of the specification that the insoluble, non-digestible and presumably therapeutic precipitate, resulting from the action of the bispecific reagent upon the therapeutic reagent, will remain in the extra-cellular fluid adjacent to the first bispecific reagent, and thus it is not clear that for example, if toxic, the precipitate will not exert its toxic affects on tissues and organs other than those of the first target cancer cells and therefore damage the unprotected host organism.
>
> Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the

disclosure how to make/use a therapeutic agent as claimed. Therefore, undue experimentation would be required to enable the claims.

Response:

The active drug produced in ADEPT is soluble and does diffuse into the systemic circulation to cause systemic toxicity which is one reason ADEPT fails (see specification at page 10). The insoluble precipitate produced by the present invention does not diffuse away (only soluble materials diffuse) and does not move away by convection into the lymphatics because tumor tissue lacks an effective lymphatic drainage (see pages 33 and 36 of specification) and if necessary the precipitate is "tethered" to various structures (see pages 36-41 of the specification).

10. Action - Section 5.(b):

"The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a bispecific reagent which will convert a first therapeutic agent into an insoluble and non-digestible precipitate at the site of the first target cancer cells. The claims are drawn to a targeting agent moiety and a first enzyme moiety, which is a non-mammalian enzyme moiety, which has a substantial affinity for the first antiagent receptor of the first target cancer cells and thus, as broadly written, read on bispecific antibodies with an antigen binding region and a non-mammalian enzyme region for the conversion of a pro-drug to a drug used for the treatment of cancer *in vivo*.

Response:

The bispecific reagent can be made by several published methods. The methods are now so standard and well known that no reference is made to them in the specification. The enzyme component of the bispecific reagent is chosen together with the soluble precipitable material so the enzyme does convert the soluble precipitable material from a soluble molecule into an insoluble precipitate. For example, penicillinase acts on lactams (penicillin) at position 3 of the indoxyls and when the penicillin is degraded by the enzyme, the indoxyl precipitates.

11. Action - Section 5.(b):

"The record contains insufficient evidence to establish that the claimed product is useful for treating human cancers. It is well known in the

art at the time the invention was made that although antibodies were highly effective as a means of selectively targeting cancer cells, antibody based targeting of therapeutics has proved relatively ineffective in the treatment of

RESPONSES TO CLAIM REJECTIONS IN SECTION 5 OF PAPER NO. 33, UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 15, SECTION 5, PAGES 2-5 OF ACTION

Action, Section 5, pages 3-4, (a')

'...a review of the cited support reveals general teachings of the chemistry of indoxyl chemistry but does not provide either guidance on or exemplification of making or using the broadly claimed agents, that would be therapeutic when administered *in vivo*. Further, the issue raised here is not only whether the making/using if soluble precipitable material is disclosed in the specification but also that the applicant has not taught how to make or use the instant invention, especially in view of Applicants (page 15, section 21 of Paper No. 14) admission on the record that the therapeutic agent is "only therapeutic after it has been converted into an insoluble material because the therapeutic effect depends on the radiation field which is generated by the precipitate induced immobilization the isotope and its long term retention at the immobilized site." A review of the specification does not reveal the absolutely critical nature of radio-labeling of the therapeutic agent...'

Response:

1. Making Soluble Precipitable Material

See the Declaration of Professor Emer. Henry Rapoport, Ph.D.

Making indoxyls as the soluble precipitable material is found in specification pages 20-23. Making the soluble precipitable material comprised of soluble and insoluble moiety is found in specification pages 23-24. The method of radio-labeling the therapeutic agent is described in the specification (page 23) and in Figs. 15-17.

2. Using Soluble Precipitable Material

See the Declaration of Professor Alan L. Epstein, M.D., Ph.D.

The method and dosages of the bispecific reagent and the therapeutic agent in the present invention are readily taught by the prior art of ADEPT disclosed in the specification. In the present invention the therapeutic agent (the soluble precipitable material) and in the prior art of ADEPT, the prodrug, are both converted by the non-mammalian enzyme moiety of a previously bound bispecific reagent. In the present invention, the therapeutic agent which is a soluble precipitable material is enzymatically converted into an insoluble precipitate. In ADEPT, a soluble pro-drug is enzymatically converted into an active soluble drug.

It is widely known and published in the field that the immobilization of radio-isotopes can be used successfully for therapy. Examples have also been given in the specification of the invention on pages 7-8, and 11. The immobilization of isotopes generates radiation fields that kill cancer cells in the immediate microregion of the deposited isotopes.

In accordance with the invention the "first therapeutic agent" (being a soluble precipitable material) is <u>not</u> therapeutic <u>per se</u> when administered *in vivo.* It only becomes therapeutic as disclosed in the specification when it is concentrated and retained <u>in situ</u>.

<u>Action, Section 5, page 4, (b'), (c'), and (d')</u>

> '...a review of pages 9 and 10 reveals the disclosure of numerous references which report the enzymatic conversion of a pro-drug to an active drug in the extracellular space, however, none of the cited references have been submitted and therefore none of the references have been considered. However, it is noted that on page 10, paragraph 2, the specification clearly states that "ADEPT approach fails to successfully treat cancer", thus dosage and methods of administration used in the prior art would not be expected to enable the instant claims, further, it is noted that the cited references are to be found in the "Prior Art" section of the

specification and that neither guidance on nor exemplification of administration or exemplification of or guidance for effective dosage are to be found in the portion of the specification drawn to the invention (c' and d'). As disclosed above the teachings on page 20-24 are drawn to indoxyl chemistry and no teaching or exemplification is provided for any of the other therapeutic reagents claimed and the argument is not found persuasive for the reasons disclosed in section (b') above,...'.

Response:

See Declaration of Professor Alan L. Epstein, M.D., Ph.D.

Applicant has included a sample of the references for ADEPT cited in the specification of the application.

Although ADEPT fails to treat cancer successfully, the dose levels of the prodrug are relevant guidelines for dose levels for the therapeutic agent and the bispecific reagent in the present invention. ADEPT fails for reasons other than the administered dose of the prodrug--most importantly because the active drug (which is produced by the enzymatic action of the enzyme moiety of the bispecific reagent converting a pro-drug into an active drug) diffuses away from its site of production to enter the blood stream where it exerts a systemic toxic effect. The larger the tumor, the larger will be the number of production sites, and the larger will be the number of active drug molecules which will diffuse into the blood to have a large systemic toxicity.

However, in the present invention, the attack against the cancer is determined by the number of radio-isotope atoms which are immobilized, which is determined by the number of enzyme molecules which are bound (via the bound bispecific reagent) and the turn-over number of the enzyme ("turn-over number" is the number of molecules that can be converted from one state to another per unit time per molecule of enzyme).

See also Applicant's response to Action, pages 3-4, (a') above.

Action, Section 5, page 4, (e')

> "...the argument is drawn to the bispecific reagent, however, as clearly repeated on page 8 of the response, the issue raised here is that the therapeutic agents may be inactivated *in vivo* and because the applicant did not distinctly and specifically point out the supposed errors rejection, the rejection is maintained,..."

Response:

The therapeutic agent is not a protein and proteolytic degradation is, therefore, not relevant. The therapeutic agent is a radio-labeled soluble precipitable material. It circulates freely in all body fluid which of course includes, as recited in official Action "fluids, cells and tissues". Since the therapeutic agent is only converted into an insoluble material by the non-mammalian enzyme moiety of the bound bispecific reagent, this is the only location where it will be immobilized and be retained for a long time, and therefore, this will be the only location where it will generate radiation fields (which destroy all cancer cells in the immediate microregion surrounding each location of the bound non-mammalian enzyme) and provide a therapeutic effect. The agent is only therapeutic after it has been converted into an insoluble material because only when immobilized, does a sufficiently large number of radio-active isotopes become deposited and be retained for a sufficiently long time. In all other locations, it may exert a minor injury and toxicity (because it is radio-labeled), but the radiation dose is not sufficient to produce a therapeutic effect. Immunological inactivation is unlikely to be an issue because the administration of the therapeutic agent will be the first time the host has been exposed to the novel agent.

Action, Section 5, pages 4, 5, (f')

> '...although the word "adapted" has indeed been replaced in the recited claims, the argument drawn to dosage and methods of administration is not found persuasive for the reasons set forth in section (b') above,...'.

Response:

See Applicant's response to "Action, section 5, page 4, (b'),(c'), and (d')" above.

Action, Section 5, page 5, (g')

> "...as recited in claim 69, the term therapeutic agent includes peptides, carbohydrates, chitosan, chitin, proteoglycans and synthetic polymers as well as indoxyl compounds and contrary to applicant's arguments, peptides, which read on proteins, and protoglycans are claimed Claim 69 specifically claims that the therapeutic agent (as identified by the claim) is converted into a extracellular precipitate which the claim defines as an insoluble and non-digestible precipitate and further Applicant admits on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitate material. (h') the argument is not persuasive for the reasons previously disclosed in the section (a') and (c') above,...".

Response:

The original claims are part of the disclosure of the application: In re Meyers (CCPA 1969) 410 F2d 420,161 USPQ 668, and the disclosure can be amended to conform with the former. Ex parte Wilson et al (POBA 1957) 116 USPQ 595. See MPEP in 608.1(1), 608.4. 706.03(o), 2163.06, 2163.06, "III"

In response to the allegation that the specification does not describe proteins and peptides, as candidates for the soluble precipitable material, applicant submits that original claim 5 recites:

> "... in which the first therapeutic agent is a soluble agent and is an organic chemical comprising at least one of peptides, including opio-melanins, of carbohydrates including cellulose, chitosan, and chitin, and of proteoglycans, of synthetic polymers, and of indoxyl compounds having molecular positions 1-7."

Action, Section 5, page 5, (h')

"...the argument is not persuasive for the reasons previously disclosed in section (sic) 5, (a') and (c') above.

Response:

See Applicant's response to "Action, Section 5, pages 3-4, (a')" above and to "Action, Section 5, page 4, (b'), (c'), and (d')" above.

Action, Section 5, page 5, (I')

> "...Applicant's stated opinion is noted but it is clear that one of skill in the art would expect that an insoluble precipitate would be removed from the claimed region either by convection, diffusion, or by phagocytosis. Applicant is invited to submit objective evidence demonstrating that the insoluble precipitate will not diffuse away, move away or be removed from the area by phagocytosis. As drawn to the tethering of the precipitate, applicant is arguing limitations not recited in the claims as presently constituted. It is noted that amendment of the claims to recite tethering limitations in an amendment submitted after final would raise a new issue not previously considered, and that the amendment would not be entered for this reason."

Response:

See Declaration of Professor Alan L. Epstein, M.D., Ph.D.

In the proposed invention, the product of the enzymatic conversion is insoluble and stable. Insoluble materials do not diffuse--only soluble materials diffuse. In the present invention, the insoluble precipitate is not removed from the area by convective flow because tumors lack effective lymphatic drainage (see references in specification pages 35-36). Further, in the present invention, the insoluble precipitate is not removed from the area by phagocytic activity because macrophage and phagocytic activity in the tumor is reduced (see references in specification pages 35-36).

For example, trypan blue adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it only remains in normal tissue for a few hours--this difference reflects the fact that normal tissues, but not cancer tissues, have an effective lymphatic drainage. Those skilled in the art would understand that this difference (hours in normal tissues and days in cancer tissue) would be amplified for insoluble materials. This is confirmed by the long term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid.

Ultimately, the insoluble precipitate will be removed by convection and phagocytosis. However, in accordance with the present invention, such removal from tumor tissue will be slower than from normal tissues. This difference is a "window of opportunity" for the therapist.

Paper 27, pag 4, line 4-13

"... (a') general methods of indoxyl chemistry, preparation of precipitable material and methods of radio labeling have been taught but the specification does not provide guidance on or exemplification of making or using the broadly claimed agents that would be therapeutic when administered *in vivo* and Applicant admits on the record that the therapeutic agent is only therapeutic after conversion. Without working examples that demonstrate that the conversion takes place *in vivo* which would provide guidance to one skilled in the art, given the issues raised in Paper No. 10, one of skill in the art could not predict that the therapeutic agent taught could be used with a reasonable expectation of success."

Paper 27, page 4, line 14-17

"... (c') Applicant is claiming a therapeutic agent, not a method for the conversion of a pro-drug to a therapeutic agent. Applicant admits on the record that the claimed therapeutic agent is not therapeutic *per se*."

Paper 27, page 5, line 16-20

"It is clear that, in the absence of objective evidence, Dr. Epstein cannot predict that the therapeutic agent will function as claimed and for the reasons previously set forth, that it cannot be predicted, in the absence of *in vivo* working examples, that the claimed therapeutic agent will function as claimed."

Paper 27, page 6, line 15-17

"Although the specification teaches how to make the soluble precipitable material cell impermeant, the specification does not teach how to use the therapeutic agent..."

Paper 27, page 6, line 21-22

"... the specification does not teach how to use the invention."

Paper 27, page 8, lin 3-5

"... in the absence of objective evidence, in view of the known unpredictability of the cancer therapeutic arts, it could not be predicted that the claimed therapeutic agent would function as claimed."

Paper 27, page 8, line 8-10 and again on page 8, line 13-15

"... the issue raised here is not that a molecule cannot be made impermeant, but rather that the specification does not teach how to use the claimed molecule so that it will function as claimed."

Paper 27, page 8, line 21 – page 9, line2

"Applicant argues that the therapeutic agent is radioactive and therefore must cause some cell damage. The arguments have been considered but have not been found persuasive because applicant is arguing limitations not recited in the claims as presently constituted."

Response 1:

The introduction of this response presented concisely the 4-step method of the claimed invention. The first therapeutic agent is converted into the first extra-cellular precipitate by the enzyme moiety of the first bispecific reagent which is bound by the first targeting agent moiety of the first bispecific reagent to the first antigenic receptor of the first target cancer cells. Continued administration of the first therapeutic reagent results in the accumulation of a large amount of first extra-cellular precipitate in the extra-cellular fluid adjacent to the first target cancer cells. The first extra-cellular precipitate has at least one of a first antigenic epitope, second antigenic epitope, and a neo-antigenic third epitope.

Thus the accumulation of the first extra-cellular precipitate is also an accumulation of the first antigenic eptitope, second antigenic epitope, and neo-antigenic third epitope. The function of the non-radiolabeled first therapeutic agent as per Claim 69 is not to kill cancer cells (i.e. it is not therapeutic *per se*), but rather to accumulate the first extra-cellular precipitate which is used as the site for the subsequent therapeutic attack delivered by the additional therapeutic agent. However, if the first therapeutic agent is radiolabeled as per Claim 83, it is therapeutic *per se* as well as serving to accumulate the first extracellular precipitate as the site for subsequent therapeutic attack delivered by the additional therapeutic agent.

The specification and the claims enable the present invention to be practiced by one of skill in the art. The specification and references for ADEPT (Publication Exhibits A and G-J, page 36, submitted with the response filed May 25, 1999) provide sufficient guidance for doses and methods of administration for the first bispecific reagent, the first therapeutic agent, and the second bispecific reagent to enable one of skill in the art to practice the present invention. In addition, the treatment of thyroid cancer with radio-iodide in particular, as well as the treatment of cancer using radio-labeled antibodies and the delivery of the pro-drug in ADEPT, provides sufficient guidance to one of skill in the art for doses and methods of administration of the radioactive toxic additional therapeutic agent to enable one of skill in the art to practice the present invention.

The well-published literature of ADEPT (which teaches the conversion of a pro-drug to an active drug by the enzyme moiety of a previously bound bispecific reagent) provides a valid working example for the present invention in which the first therapeutic agent is converted to the first extra-cellular precipitate by the enzyme moiety of the previously bound first bispecific reagent. Even in the absence of *in vivo* working examples, the disclosure in the specification of the present invention enables one of skill in the art to predict with high expectation of success, and without undue experimentation, that the first extra-cellular precipitate will form from the first therapeutic agent via the action of

the first enzyme moiety of the first bispecific reagent, and that the first extra-cellular precipitate formed from the first therapeutic agent will accumulat in the extra-cellular fluid and will function as described. (For evidence that the insoluble precipitate will be removed by convection and phagocytosis slower from tumor tissue than for normal tissue, and thus one skilled in the art is able to successfully predict that the first therapeutic agent will be retained for an extended period of time in tumor tissue and therefore function as disclosed in the present invention, please see Response 4 below.) Furthermore, Applicant has unpublished *in vitro* data produced by an independent third party (Marin Biologic of Tiburon, California) demonstrating that an immobilized enzyme (beta-galactosidase on beads in either phosphate-buffered saline or 1% agarose) converted the soluble precipitable material 4-chloro-3-indolyl-beta-D-galactopyranoside (akin to the first therapeutic agent of the present invention) to an insoluble indigo precipitate.

The following sample calculation illustrates how the specification and references for the working example of ADEPT, plus the working example of the 90%-curative treatment of thyroid cancer by the administration and immobilization of radio-iodide, provide sufficient guidance to one of skill in the art for doses and methods of administration of the first bispecific reagent, first therapeutic agent, second bispecific reagent, and radioactive toxic additional therapeutic agent of the present invention:

(1) Re: the current 90%-curative treatment of thyroid cancer with radio-iodide for 10 grams of tumor:

An attempt is made to accumulate 10(4) -- that is, ten thousand -- Iodine-131 atoms per cancer cell. This translates to 3x10(14) isotope atoms per 10 grams of tumor {10 grams X 3x10(9) cells per gram X 10(4) isotope atoms per cell}. The isotopes circulates with a biological half-life of approximately 3-10 hours (10 hours is used for these calculations) and remains in the tumor with a biological half-life of 1-3 days (3 days is used for the

calculations). A low test dose of isotope and measuring thyroid uptake and blood levels determines the required therapeutic dose of isotope; there is NO standard uniform therapeutic dose which is used.

(2) Re: the present invention for 10 grams of tumor:

(a) 10 grams of tumor contain 3x10(9) cells.

(b) There are 10(4)-10(5) non-endocytosing receptors per cell {10(5) receptors per cell is used for these calculations}.

(c) Multiplying (a) X (b), there are 3x10(14) non-endocytosing receptors per 10 grams of tumor.

(d) Approximately 1% {10(-2)} of the administered dose of an antibody targeting agent binds to 10 grams of tumor.

(e) Using (c) and (d), 3x10(16) {= 3 x10(14) X 10(2)} (antibody) first targeting agent moiety molecules must be administered to bind one molecule to each non-endocytosing receptor.

(f) Since each first targeting agent moiety molecule has attached to it one non-mammalian first enzyme moiety molecule (forming the first bispecific reagent), there will be 3x10(14) first enzyme moiety molecules bound per 10 grams of tumor after the bispecific reagent has been administered and allowed to bind to the non-endocytosing receptors.

(g) The turnover number of the first enzyme moiety (= rate of enzyme conversion of substrate into product) is approximately 10(2) per second or more.

(h) Since there are approximately 10(5) seconds per day, 3x10(14) first enzyme moiety molecules will convert 3x10(21) first therapeutic agent molecules to first extra-cellular precipitate molecules per day {3x10(14) first enzyme moiety molecules X 10(5) seconds per day X 10(2) per second turnover number of enzyme}. Thus, after administering the first bispecific reagent followed by the first therapeutic agent, there will be 3x10(21) molecules of insoluble non-digestible first extra-cellular precipitate with antigenic

epitopes per 10 grams of tumor. {Note that if the first therapeutic agent is radio-labeled as per Claim 83, then 3x10(21) radioactive first extracellular precipitate molecules will be retained per 10 grams of tumor}.

(i) Following the reasoning above, the second bispecific reagent (which consists of a targeting agent moiety specific for one of the antigenic epitopes on the first extra-cellular precipitate plus a non-mammalian second enzyme moiety) is administered in sufficient quantity to bind one molecule of it to each molecule of first extra-cellular precipitate (via the antigenic epitopes on the precipitate).

(j) 3x10(21) second enzyme moiety molecules will convert 3x10(26) molecules of soluble radioactive additional therapeutic agent to the radioactive toxic new form per day {= approximately 1.5 x10 (26) molecules per 10 hours for comparison to the thyroid cancer treatment model in (1) above}, and the radioactive toxic new form will remain in the extra-cellular fluid of the tumor with a biological half-life of at least 3 days (this is a conservative estimate and is the same as the biological half-life in the thyroid cancer model described above).

Thus the present invention has the potential to deposit and retain 5x10(11) times as many radioactive molecules in the tumor than does the 90%-curative treatment of thyroid cancer with radio-iodide {1.5x10(26) molecules versus 3x10(14) molecules}.

In actual practice, the number of isotope atoms deposited in the present invention is likely to be less than 1.5x10(26) per 10 hours because of a number of factors such as (a) steric hindrance, (b) macrophage uptake and convective flow into lymphatics of the first extra-cellular precipitate and the radioactive toxic new form, (c) endogenous antibody molecules which bind to the cell receptors and therefore compete with the administered first bispecific reagent, (d) complexing of the first targeting agent moiety of the first bispecific reagent with soluble cell receptors in the circulation, such complexes being quickly engulfed by macrophages of the liver, lung and spleen, and (e) loss of bispecific reagent bound to the receptors over time.

However, the huge potential excess of radioactive molecule deposition compared to thyroid cancer treatment (combined with the conservative estimate of the retention time of the radioactive toxic new form in the tumor, and the short duration of time necessary for the isotope to circulate in the blood) should enable the present invention to achieve micro-regional destruction of tumor cells with minimal systemic radioactive toxicity.

See also Mayers declaration.

Paper 27, page 4, line 13-14

"... (b') applicant is arguing limitations not present in the claims as currently constituted as immobilization of a radioisotope is not claimed."

Paper 27, page 4, line 17-19

"... (d') applicant is arguing limitations not recited in the claims as presently constituted as the claims are not drawn to immobilized radio-isotope atoms."

Response 2:

The introduction of this response presented concisely the 4-step method of the claimed invention, including how the first therapeutic agent is used principally to generate a non-toxic first extra-cellular precipitate as the site for the subsequent therapeutic attack delivered by the additional therapeutic agent. Independent claim 69 discloses the composition of the first therapeutic agent, and dependent claim 83 is a limitation of claim 69 wherein the first therapeutic agent is radio-labeled. Using a radio-labeled first therapeutic agent is claimed in the present invention and is disclosed in the specification, including methods of radio-labeling (page 23). The conversion of a radio-labeled first therapeutic agent would result in the formation of a radio-labeled first extra-cellular precipitate. Since the first extra-cellular precipitate is insoluble and therefore remains in

the extra-cellular fluid for an extended period of time, the present invention does in fact claim the immobilization of a radioisotope. (Applicant also claims immobilization of a radioisotope when the second therapeutic agent is converted to the radioactive toxic new form.)

Paper 27, page 4, line 19 – page 5, line 6

"... (e') it is clear that the limitation that the therapeutic agent is not a protein is not recited in the claims as presently constituted and further, other than claim 83, none of the claims are drawn to radio-labeled soluble precipitable material and none of the claims are drawn to immobilized reagents. Without working examples, in view of the issues raised in Paper No. 10, one of skill in the art could not predict that the only location where the therapeutic agent will be immobilized will be at the site of the bispecific reagent, (f') the issue raised here was not that the specification does not describe protein and peptides as candidates for the soluble precipitable material but that Applicant's response was confusing because Applicant states on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitable material."

Response 3:

The Examiner is correct that Applicant's response that "The therapeutic agent is not a protein ..." was confusing, in light of Claim 69 which states "... the first therapeutic agent comprising at least one organic chemical of at least one of peptides, including opio-melanins ..." The response should have stated that "The therapeutic agent is not a readily degradable protein ..." and proteolytic degradation is, therefore, not relevant. Certain peptides such as prion proteins, amyloid of Alzheimer's disease, and keratins are quite non-degradable. In the case of the named opio-melanins, although the peptide portion may be degradable, the remaining melanin portion is quite non-degradable.

Regarding claims drawn to immobilized reagents, please see Response 2 above.

Regarding the location where the therapeutic agent will be immobilized, as disclosed in the claims and specification of the present invention (Specification, page 17, 19-24), the conversion of the first therapeutic agent can only occur via the action of the first enzyme moiety of the first bispecific reagent. The conversion of the first therapeutic agent into the insoluble first extracellular precipitate by the first enzyme moiety of the previously bound first bispecific reagent is analogous to the prior art of ADEPT wherein a soluble prodrug is converted by the enzyme moiety of a previously bound bispecific reagent into an active drug (Specification, p. 9-10 and Publication Exhibits for ADEPT (A and G-J) submitted with the response filed May 25, 1999, page 36). Just as the pro-drugs of ADEPT are adapted to be converted to active drugs only by the enzyme moiety of the previously bound bispecific reagent, so the first therapeutic agent of the present invention is adapted to be converted to the first extra-cellular precipitate only by the first enzyme moiety of the previously bound first bispecific reagent. Thus, even in the absence of *in vivo* working examples, the disclosure in the specification enables one of skill in the art to predict that the only location where the first therapeutic agent will be immobilized will be at the site of the first enzyme moiety of the first bispecific reagent, because that is the only location at which the first therapeutic agent will be converted into the insoluble first extra-cellular precipitate and therefore be immobilized; at all other sites the first therapeutic agent will remain soluble and therefore diffuse away and be rapidly excreted.

See also Rapoport Declaration.
See also Mayers Declaration.

Paper 27, page 5, line 6-10

"... (g') Applicant was invited to submit objective evidence to resolve this issue, no objective evidence has been submitted but Applicant has admitted on the record that 'ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues.'"

Paper 27, page 5, line 23 – page 6, lin 7

"Dr. Epstein states that insoluble DNA is retained much longer in tumor tissue compared to normal tissue and that one skilled in the art would readily recognize that the insoluble precipitate formed in Dr. Rose's invention will be retained in the same way. The argument has been considered but has not been found persuasive because it is clear that, although retained longer, the insoluble precipitate will be removed. It cannot be determined or predicted from the information in the specification or in the art of record that the invention will function as claimed."

Response 4:

The Publication Exhibits showing the absence of lymphatic drainage and the inhibition of macrophages in the tumor (Publication Exhibits B and C, page 36 submitted with the response filed May 25, 1999), as well as the specification (page 35-36), provide sufficient guidance to enable one skilled in the art to successfully predict, without undue experimentation, that the first therapeutic agent will function as disclosed in the present invention, and that the first extra-cellular precipitate will remain in the tumor tissue longer than normal tissue (i.e. will be removed from tumor tissue more slowly), and furthermore that the first extra-cellular precipitate will remain in the tumor tissue for sufficient time for the present invention to be practiced. For example, trypan blue adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it remains in normal tissue for only a few hours – this difference reflects the fact that normal tissues, but not cancer tissues, have an effective lymphatic drainage. Those skilled in the art would understand that this difference (days in cancer tissues versus hours in normal tissues) would be amplified for insoluble materials. This is confirmed by the long-term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid. While it is true that the extra-cellular precipitate of the present invention will eventually be removed by phagocytosis or convective flow, it

need remain in the extra-cellular fluid f the cancer only for a matter of days in order for the present invention to be practiced (see Response 1).

See also Mayers declaration.

RESPONSE TO CLAIM REJECTIONS IN SECTION 5 OF PAPER NO. 33, UNDER 35 USC SECTION 112, BASED UPON PAPER NO. 10, SECTION 5(b), PAGES 8-10

10. Action - Section 5.(b):

> "The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a bispecific reagent which will convert a first therapeutic agent into an insoluble and non-digestible precipitate at the site of the first target cancer cells. The claims are drawn to a targeting agent moiety and a first enzyme moiety, which is a non-mammalian enzyme moiety, which has a substantial affinity for the first antiagent receptor of the first target cancer cells and thus, as broadly written, read on bispecific antibodies with an antigen binding region and a non-mammalian enzyme region for the conversion of a pro-drug to a drug used for the treatment of cancer *in vivo*.

Response:

The bispecific reagent can be made by several published methods. The methods are now so standard and well known that no reference is made to them in the specification. The enzyme component of the bispecific reagent is chosen together with the soluble precipitable material so the enzyme does convert the soluble precipitable material from a soluble molecule into an insoluble precipitate. For example, penicillinase acts on lactams (penicillin) at position 3 of the indoxyls and when the penicillin is degraded by the enzyme, the indoxyl precipitates.

11. Action - Section 5.(b):

> "The record contains insufficient evidence to establish that the claimed product is useful for treating human cancers. It is well known in the art at the time the invention was made that although antibodies were highly effective as a means of selectively targeting cancer cells, antibody based targeting of therapeutics has proved relatively ineffective in the treatment of solid tumors such as carcinomas. WO 93/17715 specifically teaches that (1) solid tumors are generally impermeable to antibody-sized molecules; (2) that antibodies that enter the tumor mass do not distribute evenly because

of the dense packing of tumor cells; and (3) antigen-deficient mutants can escape being killed by the antibody-based therapies and regrow (p. 4, lines 10-37), thus the ability to use the claimed bispecific reagent would be highly unpredictable."

Response:

The present invention was specifically made to circumvent the problems described in the Action quoted above. The first two problems, tumors impermeable to antibodies and lack of uniform distribution of the antibodies, are relevant to ADEPT, referred to above, which only partially circumvents these problems. The present invention completely circumvents these two problems because it does not matter how slowly the bispecific reagent penetrates into the tumor. The problem of antigenic deficient mutants is circumvented to some extent by ADEPT (see page 10 of the specification); however the problem is even more effectively circumvented by the present invention because the process simulates the successful treatment of thyroid cancer and creates intense radiation fields which kill all cells in each microregion including antigen deficient mutants (see pages 7, 11, and 33-34 of the specification).

12. Action - Section 5.(b):

"Further, the specification does not provide teachings to establish effective dosages or methods of administration of any of the claimed bispecific reagents. In addition, the bispecific reagent may be inactivated *in vivo* before producing a therapeutic effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to ne skilled inthe art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed therapeutic agent with a reasonable expectation of success."

Response:

The dosage method of administration, and the inactivation of the bispecific reagents are the same as in ADEPT which has circumvented the problems (see pages 9 and 10 of the specification). One skilled in the art who knows ADEPT would readily recognize the increase efficacy of the present invention over ADEPT.

13. Action - Section 5.(b):

In addition, Applicant claims (claim 76) a first therapeutic agent selected from the group including indoxyl-lactam which is cleavable by the first enzyme moiety of the first bispecific reagent. Thus, it appears that

the action of the non-mammalian enzyme on the first therapeutic agent is to render it nontherapeutic and, clearly, undue experimentation would be required to enable the claims.

Response:

Loss of antibacterial activity by the action of lactamase is certain to develop; however, with respect to the present invention, this loss is irrelevant, or more correctly, is actually required to convert a soluble indoxyl lactam into an insoluble, indigoid material.

14. Action - Section 5.(b):

"The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent, the cell-impermeant chemical causing the first therapeutic agent to be cell impermeant (claim 71). The record contains insufficient evidence to establish that the claimed product is useful for treating human cancers."

Response:

Making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22, and 29-30 of the specification.

15. Action - Section 5.(b):

The specification gives no guidance on or exemplification of how to choose the agent to be attached to the broadly claimed first therapeutic agent or how or where to attach it.

Response:

Making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22, and 29-30 of the specification.

16. Action - Section 5.(d):

The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent to be cell impermeant wherein the cell impermeant chemical is selected from the group including materials having molecular weight greater than 1000 daltons (claim 72). Clearly, as broadly written, the claim reads on any chemical that is

greater than 1000 daltons and just as clearly, the specification has not taught how to make or us any therapeutic reagent conjugated to any chemical of unlimited molecular weight.

Response:

Making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22, and 29-30 of the specification. The recitation of materials having a molecular weight of greater than 1000 dollars defines a large molecule and thereby a cell impermeant chemical.

RESPONSE TO CLAIM REJECTIONS IN SECTION 6 OF PAPER NO. 33, UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 15, SECTION 6, PAGES 5-6

Action, Section 6, page 6, (a')

"...because the issue raised here is not whether the instant invention circumvents problems related to impermeability of tumors to antibodies and lack of uniform distribution of antibodies, but rather whether the instant specification is enabling. For the reasons stated, one of skill in the art would be forced into undue experimentation to practice the claimed invention,...".

Response:

See Applicant's response to "Action, Section 5, page 4 (b'), (c'), and (d')" above.

Action, Section 6, page 6, (b')

"... for the reason previously disclosed in Section 5(b') above,..."

Response:

See Applicant's response to "Action, Section 6, page 6, (a')" above.

Action, Section 6, page 6, (c')

"...a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p. 19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecule on page 22 and 29-30."

Response:

The specification in referring to making the soluble precipitable material cell impermeant on page 19 recites that "the first therapeutic agent can be made cell impermeant by attaching one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 Daltons and anionic chemicals including thiols."

See also Applicant's response to "Action, Section 8, page 7" below.

RESPONSE TO CLAIM REJECTIONS IN SECTION 6 OF PAPER NO. 33
UNDER 35 USC, SECTION 112, BASED UPON PAPER NO. 27,
SECTION 7, PAGES 6-7

Paper 27, page 6, line 15-17

"Although the specification teaches how to make the soluble precipitable material cell impermeant, the specification does not teach how to use the therapeutic agent..."

Paper 27, page 6, line 21-22

"... the specification does not teach how to use the invention."

Response 1:

The introduction of this response presented concisely the 4-step method of the claimed invention. The first therapeutic agent is converted into the first extra-cellular precipitate by the enzyme moiety of the first bispecific reagent which is bound by the first targeting agent moiety of the first bispecific reagent to the first antigenic receptor of the first target cancer cells. Continued administration of the first therapeutic reagent results in the accumulation of a large amount of first extra-cellular precipitate in the extra-cellular fluid adjacent to the first target cancer cells. The first extra-cellular precipitate has at least one of a first antigenic epitope, second antigenic epitope, and a neo-antigenic third epitope.

Thus the accumulation of the first extra-cellular precipitate is also an accumulation of the first antigenic eptitope, second antigenic epit pe, and neo-antigenic third epitope. The function of the non-radiolabeled first therapeutic agent as per Claim 69 is not to kill cancer cells (i.e. it is not therapeutic *per se*), but rather to accumulate the first extra-cellular precipitate which is used as the site for the subsequent therapeutic attack delivered by the additional therapeutic agent. However, if the first therapeutic agent is radiolabeled as per Claim 83, it is therapeutic *per se* as well as serving to accumulate the first extracellular precipitate as the site for subsequent therapeutic attack delivered by the additional therapeutic agent.

The specification and the claims enable the present invention to be practiced by one of skill in the art. The specification and references for ADEPT (Publication Exhibits A and G-J, page 36, submitted with the response filed May 25, 1999) provide sufficient guidance for doses and methods of administration for the first bispecific reagent, the first therapeutic agent, and the second bispecific reagent to enable one of skill in the art to practice the present invention. In addition, the treatment of thyroid cancer with radio-iodide in particular, as well as the treatment of cancer using radio-labeled antibodies and the delivery of the pro-drug in ADEPT, provides sufficient guidance to one of skill in the art for doses and methods of administration of the radioactive toxic additional therapeutic agent to enable one of skill in the art to practice the present invention.

The well-published literature of ADEPT (which teaches the conversion of a pro-drug to an active drug by the enzyme moiety of a previously bound bispecific reagent) provides a valid working example for the present invention in which the first therapeutic agent is converted to the first extra-cellular precipitate by the enzyme moiety of the previously bound first bispecific reagent. Even in the absence of *in vivo* working examples, the disclosure in the specification of the present invention enables one of skill in the art to predict with high expectation of success, and without undue experimentation, that the

first extra-cellular precipitate will form from the first therapeutic agent via the action of the first enzyme moiety of the first bispecific reagent, and that the first extra-cellular precipitate formed from the first therapeutic ag nt will accumulate in the extra-cellular fluid and will function as described. (For evidence that the insoluble precipitate will be removed by convection and phagocytosis slower from tumor tissue than for normal tissue, and thus one skilled in the art is able to successfully predict that the first therapeutic agent will be retained for an extended period of time in tumor tissue and therefore function as disclosed in the present invention, please see Response 4 below.) Furthermore, Applicant has unpublished *in vitro* data produced by an independent third party (Marin Biologic of Tiburon, California) demonstrating that an immobilized enzyme (beta-galactosidase on beads in either phosphate-buffered saline or 1% agarose) converted the soluble precipitable material 4-chloro-3-indolyl-beta-D-galactopyranoside (akin to the first therapeutic agent of the present invention) to an insoluble indigo precipitate.

The following sample calculation illustrates how the specification and references for the working example of ADEPT, plus the working example of the 90%-curative treatment of thyroid cancer by the administration and immobilization of radio-iodide, provide sufficient guidance to one of skill in the art for doses and methods of administration of the first bispecific reagent, first therapeutic agent, second bispecific reagent, and radioactive toxic additional therapeutic agent of the present invention:

(1) Re: the current 90%-curative treatment of thyroid cancer with radio-iodide for 10 grams of tumor:

An attempt is made to accumulate 10(4) -- that is, ten thousand -- Iodine-131 atoms per cancer cell. This translates to 3x10(14) isotope atoms per 10 grams of tumor {10 grams X 3x10(9) cells per gram X 10(4) isotope atoms per cell}. The isotopes circulates with a biological half-life of approximately 3-10 hours (10 hours is used for these calculations)

and remains in the tumor with a biological half-life of 1-3 days (3 days is used for the calculations). A low test dose of isotope and measuring thyroid uptake and blood levels determines the required therapeutic dose of isotope; there is NO standard uniform therapeutic dose which is used.

(2) Re: the present invention for 10 grams of tumor:

(a) 10 grams of tumor contain 3x10(9) cells.

(b) There are 10(4)-10(5) non-endocytosing receptors per cell {10(5) receptors per cell is used for these calculations}.

(c) Multiplying (a) X (b), there are 3x10(14) non-endocytosing receptors per 10 grams of tumor.

(d) Approximately 1% {10(-2)} of the administered dose of an antibody targeting agent binds to 10 grams of tumor.

(e) Using (c) and (d), 3x10(16) {= 3 x10(14) X 10(2)} (antibody) first targeting agent moiety molecules must be administered to bind one molecule to each non-endocytosing receptor.

(f) Since each first targeting agent moiety molecule has attached to it one non-mammalian first enzyme moiety molecule (forming the first bispecific reagent), there will be 3x10(14) first enzyme moiety molecules bound per 10 grams of tumor after the bispecific reagent has been administered and allowed to bind to the non-endocytosing receptors.

(g) The turnover number of the first enzyme moiety (= rate of enzyme conversion of substrate into product) is approximately 10(2) per second or more.

(h) Since there are approximately 10(5) seconds per day, 3x10(14) first enzyme moiety molecules will convert 3x10(21) first therapeutic agent molecules to first extra-cellular precipitate molecules per day {3x10(14) first enzyme moiety molecules X 10(5) seconds per day X 10(2) per second turnover number of enzyme}. Thus, after administering the

first bispecific reagent followed by the first therapeutic agent, there will be 3x10(21) molecules of insoluble non-digestible first extra-cellular precipitate with antigenic epitopes per 10 grams of tumor. {Note that if the first therapeutic agent is radio-labeled as per Claim 83, then 3x10(21) radioactive first extracellular precipitate molecules will be retained per 10 grams of tumor}.

(i) Following the reasoning above, the second bispecific reagent (which consists of a targeting agent moiety specific for one of the antigenic epitopes on the first extra-cellular precipitate plus a non-mammalian second enzyme moiety) is administered in sufficient quantity to bind one molecule of it to each molecule of first extra-cellular precipitate (via the antigenic epitopes on the precipitate).

(j) 3x10(21) second enzyme moiety molecules will convert 3x10(26) molecules of soluble radioactive additional therapeutic agent to the radioactive toxic new form per day {= approximately 1.5 x10 (26) molecules per 10 hours for comparison to the thyroid cancer treatment model in (1) above}, and the radioactive toxic new form will remain in the extra-cellular fluid of the tumor with a biological half-life of at least 3 days (this is a conservative estimate and is the same as the biological half-life in the thyroid cancer model described above).

Thus the present invention has the potential to deposit and retain 5x10(11) times as many radioactive molecules in the tumor than does the 90%-curative treatment of thyroid cancer with radio-iodide {1.5x10(26) molecules versus 3x10(14) molecules}.

In actual practice, the number of isotope atoms deposited in the present invention is likely to be less than 1.5x10(26) per 10 hours because of a number of factors such as (a) steric hindrance, (b) macrophage uptake and convective flow into lymphatics of the first extra-cellular precipitate and the radioactive toxic new form, (c) endogenous antibody molecules which bind to the cell receptors and therefore compete with the administered first bispecific reagent, (d) complexing of the first targeting agent moiety of the first

bispecific reagent with soluble cell receptors in the circulation, such complexes being quickly engulfed by macrophages of the liver, lung and spleen, and (e) loss of bispecific reagent bound to the receptors over time.

However, the huge potential excess of radioactive molecule deposition compared to thyroid cancer treatment (combined with the conservative estimate of the retention time of the radioactive toxic new form in the tumor, and the short duration of time necessary for the isotope to circulate in the blood) should enable the present invention to achieve micro-regional destruction of tumor cells with minimal systemic radioactive toxicity.

See also Mayers declaration.

Response 2:

The introduction of this response presented concisely the 4-step method of the claimed invention, including how the first therapeutic agent is used principally to generate a non-toxic first extra-cellular precipitate as the site for the subsequent therapeutic attack delivered by the additional therapeutic agent. Independent claim 69 discloses the composition of the first therapeutic agent, and dependent claim 83 is a limitation of claim 69 wherein the first therapeutic agent is radio-labeled. Using a radio-labeled first therapeutic agent is claimed in the present invention and is disclosed in the specification, including methods of radio-labeling (page 23). The conversion of a radio-labeled first therapeutic agent would result in the formation of a radio-labeled first extra-cellular precipitate. Since the first extra-cellular precipitate is insoluble and therefore remains in the extra-cellular fluid for an extended period of time, the present invention does in fact claim the immobilization of a radioisotope. (Applicant also claims immobilization of a radioisotope when the second therapeutic agent is converted to the radioactive toxic new form.)

Response 3:

The Examiner is correct that Applicant's response that "The therapeutic agent is not a protein ..." was confusing, in light of Claim 69 which states "... the first therapeutic agent comprising at least one organic chemical of at least one of peptides, including opio-melanins ..." The response should have stated that "The therapeutic agent is not a readily degradable protein ..." and proteolytic degradation is, therefore, not relevant. Certain peptides such as prion proteins, amyloid of Alzheimer's disease, and keratins are quite non-degradable. In the case of the named opio-melanins, although the peptide portion may be degradable, the remaining melanin portion is quite non-degradable.

Regarding claims drawn to immobilized reagents, please see Response 2 above.

Regarding the location where the therapeutic agent will be immobilized, as disclosed in the claims and specification of the present invention (Specification, page 17, 19-24), the conversion of the first therapeutic agent can only occur via the action of the first enzyme moiety of the first bispecific reagent. The conversion of the first therapeutic agent into the insoluble first extracellular precipitate by the first enzyme moiety of the previously bound first bispecific reagent is analogous to the prior art of ADEPT wherein a soluble prodrug is converted by the enzyme moiety of a previously bound bispecific reagent into an active drug (Specification, p. 9-10 and Publication Exhibits for ADEPT (A and G-J) submitted with the response filed May 25, 1999, page 36). Just as the pro-drugs of ADEPT are adapted to be converted to active drugs only by the enzyme moiety of the previously bound bispecific reagent, so the first therapeutic agent of the present invention is adapted to be converted to the first extra-cellular precipitate only by the first enzyme moiety of the previously bound first bispecific reagent. Thus, even in the absence of *in vivo* working examples, the disclosure in the specification enables one of skill in the art to predict that the only location where the first therapeutic agent will be immobilized will be at the site of the first enzyme moiety of the first bispecific reagent, because that is the only location at which the first therapeutic agent will be converted into the insoluble first

extra-cellular precipitate and therefore be immobilized; at all other sites the first therapeutic agent will remain soluble and therefore diffuse away and be rapidly excreted.

See also Rapoport Declaration.

See also Mayers Declaration.

Response 4:

The Publication Exhibits showing the absence of lymphatic drainage and the inhibition of macrophages in the tumor (Publication Exhibits B and C, page 36 submitted with the response filed May 25, 1999), as well as the specification (page 35-36), provide sufficient guidance to enable one skilled in the art to successfully predict, without undue experimentation, that the first therapeutic agent will function as disclosed in the present invention, and that the first extra-cellular precipitate will remain in the tumor tissue longer than normal tissue (i.e. will be removed from tumor tissue more slowly), and furthermore that the first extra-cellular precipitate will remain in the tumor tissue for sufficient time for the present invention to be practiced. For example, trypan blue adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it remains in normal tissue for only a few hours – this difference reflects the fact that normal tissues, but not cancer tissues, have an effective lymphatic drainage. Those skilled in the art would understand that this difference (days in cancer tissues versus hours in normal tissues) would be amplified for insoluble materials. This is confirmed by the long-term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid. While it is true that the extra-cellular precipitate of the present invention will eventually be removed by phagocytosis or convective flow, it need remain in the extra-cellular fluid of the cancer only for a matter of days in order for the present invention to be practiced (see Response 1).

See also Mayers declaration.

Response 5:

According to the Merck Index, all of the drugs listed on Page 9 Lines 14-17 of International Publication No. WO 91/19134 dated 27 JUN 1991 are soluble except melphalan, which is insoluble but does not undergo a soluble to insoluble conversion as does the first therapeutic agent of the present invention. Furthermore, it would be expected by one skilled in the art that the recited pro-drugs when converted into active drugs were soluble, because such non-radioactive drugs must be soluble in order to diffuse through the cancer and thus have more than an extremely limited localized effect (i.e. have a "bystander effect"). Furthermore, none of the recited pro-drugs were therapeutically radioactive, because there is no way to make a therapeutically radioactive pro-drug inherently less toxic than the active drug to which it is converted. Only by causing extended retention time of a radioactive pro-drug (as caused by the soluble-to-insoluble conversion of the first and additional therapeutic agents of the present invention) can the pro-drug be made less toxic than the active drug.

Response 6:

Applicant did in fact, in the amendment, include the deletion of the indefinite term "derivatives." The relevant text in the amendment filed January 13, 1997 (pages 3-4) read as follows: "79. (twice amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes benzyloxy compounds [and derivatives of benzyloxy compounds] attached at position 5 of the indoxyl compounds to [alter the solubility, digestibility, color, and physical state] reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by at least one of diffusion and convective flow in the extracellular fluid."

RESPONSES TO CLAIM REJECTIONS IN SECTION 7 OF PAPER NO. 33
UNDER 35 USC, SECTION 112, FIRST PARAGRAPH, BASED UPON
PAPER NO. 10, SECTION 5 (c), PAGE 10, AND SECTION 5 (d), PAGE 11

Response In the response to the Official Action, applicant argues that the method of making a soluble precipitable material into a cell impermeant molecule is disclosed in the specifications on pages 19, 22 and 29-30. On page 19 of the '590 application, applicant describes the need for the therapeutic agent to be cell impermeant and further describes how cell impermeance can be readily achieved by attaching to the therapeutic agent "one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 daltons and anionic chemicals including thiols."

As disclosed on page 4 in the declaration of Professor Henry Rapoport submitted in support of the applicant's response on May 25, 1999, the practice of attaching molecules, such as polymers or peptides with a molecular weight of greater than 1,000 daltons and/or making materials anionic, is frequently practiced. Further the declaration of Professor Rapoport argues that sufficient information about the chemistry of the soluble precipitable material is disclosed in the specification of the '590 application to enable one skilled in the art to attach such molecules to the soluble precipitable material.

Finally, as disclosed on pages 7 and 8 in the declaration of Professor Alan Epstein submitted in support of the applicant's response on May 25, 1999, it is well known to one skilled in the art that "the attachment of large and/or anionic molecules to a product will make the resultant product cell impermeant." Further the declaration of Professor Epstein describes how the attachment of such molecules to achieve cell impermeance of various products is widely published and frequently used. Thus, one skilled in the art would readily expect the soluble precipitable material disclosed in the present invention to become cell impermeant and function as described in the specifications and claims if a polymer or peptide with a molecular size greater than 1,000 daltons were attached.

(Action, Paper No. 10, Section 5(d), page 11
18, 1998)

"The specification gives no guidance on or exemplification, either *in vivo* or *in vivo*, of making, using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent, the cell impermeant

chemical causing the first therapeutic agent to be cell impermeant wherein the cell impermeant chemical is selected from the group including materials having a molecular weight greater than 1000 daltons (claim 72). Clearly, as broadly written, the claim reads on any chemical that is greater than 1000 daltons and just as clearly, the specification has not taught how to make or use any therapeutic reagent conjugated to any chemical of unlimited molecular weight. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from

In the response to the Official Action Applicant argues that the method of making a soluble precipitable material into a cell impermeant molecule is disclosed in the specification on pages 19, 22, and 29-30. On page 19 of the specification, Applicant describes the need for the therapeutic agent to be cell impermeant and further describes how cell impermeant can be readily achieved by attaching to the therapeutic agent "one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 daltons and anionic chemicals including thiols."

As disclosed on page 4 in the Declaration of Professor Emer. Henry Rapoport, dated May 24, 1999 and submitted in support of Applicant's Amendment, filed on May 25, 1999, the practice of attaching molecules, such as polymers or peptides with a molecular weight of greater than 1,000 daltons and/or making materials anionic, is frequently practiced. Further the Declaration of Professor Emer. Henry Rapoport argues that sufficient information about the chemistry of the soluble precipitable material is disclosed in the specification of the application to enable one of skill in the art to attach such molecules to the soluble precipitable material.

Action - Section 5.(e):

"The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent, the cell-impermeant chemical causing the first therapeutic agent to be cell impermeant (claim 71). The record contains insufficient evidence to establish that the claimed product is useful for treating human cancers."

Response:

Making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22, and 29-30 of the specification.

Action - Section 5.(b):

The specification gives no guidance on or exemplification of how to choose the agent to be attached to the broadly claimed first therapeutic agent or how or where to attach it.

Response:

Making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22, and 29-30 of the specification.

Action - Section 5.(d):

The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent to be cell impermeant wherein the cell impermeant chemical is selected from the group including materials having molecular weight greater than 1000 daltons (claim 72). Clearly, as broadly written, the claim reads on any chemical that is greater than 1000 daltons and just as clearly, the specification has not taught how to make or use any therapeutic reagent conjugated to any chemical of unlimited molecular weight.

Response:

Making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22, and 29-30 of the specification. The recitation of materials having a molecular weight of greater than 1000 dollars defines a large molecule and thereby a cell impermeant chemical.

RESPONSES TO CLAIM REJECTIONS IN SECTION 7 OF PAPER NO. 33, UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 18 (NOT PAPER NO. 15), SECTION 8, PAGE 7 OF ACTION

Action, Section 8, page 7

"Applicant argues that making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22, and 29-30.
The argument has been noted but has not been found persuasive."

Response:

See Applicant's response to "Action, Section 8, page 7," below.

Action, Section 8, page 7

"Applicant argues that making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22 and 29-30. The recitation of materials having a molecular weight of greater than 1000 Daltons defines a large molecule and thereby a cell impermeant chemical. The argument has been noted, but has not been found persuasive for the reasons disclosed in 6(c') above. Further, the issue raised here was not the definition of a large molecule that is cell impermeant but rather the issue raised was how to use a large molecule, as broadly claimed, that will function as claimed."

Response:

See Declaration of Professor Emer. Henry Rapoport and Declaration of Professor Alan L. Epstein, M.D., Ph.D.

RESPONSES TO CLAIM REJECTIONS IN SECTION 8 OF PAPER NO. 33 UNDER 35 USC, SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 27, SECTION 8, PAGES 7-8 OF ACTION

Paper 27, page 8, line 3-5

"... in the absence of objective evidence, in view of the known unpredictability of the cancer therapeutic arts, it could not be predicted that the claimed therapeutic agent would function as claimed."

Paper 27, page 8, line 8-10 and again on page 8, line 13-15

"... the issue raised here is not that a molecule cannot be made impermeant, but rather that the specification does not teach how to use the claimed molecule so that it will function as claimed."

Paper 27, page 8, line 21 – page 9, line2

"Applicant argues that the therapeutic agent is radioactive and therefore must cause some cell damage. The arguments have been considered but have not been found persuasive

because applicant is arguing limitations not recited in the claims as presently constituted."

Response 1:

The introduction of this response presented concisely the 4-step method of the claimed invention. The first therapeutic agent is converted into the first extra-cellular precipitate by the enzyme moiety of the first bispecific reagent which is bound by the first targeting agent moiety of the first bispecific reagent to the first antigenic receptor of the first target cancer cells. Continued administration of the first therapeutic reagent results in the accumulation of a large amount of first extra-cellular precipitate in the extra-cellular fluid adjacent to the first target cancer cells. The first extra-cellular precipitate has at least one of a first antigenic eptitope, second antigenic epitope, and a neo-antigenic third epitope. Thus the accumulation of the first extra-cellular precipitate is also an accumulation of the first antigenic eptitope, second antigenic epitope, and neo-antigenic third epitope. The function of the non-radiolabeled first therapeutic agent as per Claim 69 is not to kill cancer cells (i.e. it is not therapeutic *per se*), but rather to accumulate the first extra-cellular precipitate which is used as the site for the subsequent therapeutic attack delivered by the additional therapeutic agent. However, if the first therapeutic agent is radiolabeled as per Claim 83, it is therapeutic *per se* as well as serving to accumulate the first extracellular precipitate as the site for subsequent therapeutic attack delivered by the additional therapeutic agent.

The specification and the claims enable the present invention to be practiced by one of skill in the art. The specification and references for ADEPT (Publication Exhibits A and G-J, page 36, submitted with the response filed May 25, 1999) provide sufficient guidance for doses and methods of administration for the first bispecific reagent, the first therapeutic agent, and the second bispecific reagent to enable one of skill in the art to

practice the present invention. In addition, the treatment of thyroid cancer with radio-iodide in particular, as well as the treatment of cancer using radio-labeled antibodies and the delivery of the pro-drug in ADEPT, provides sufficient guidance to one of skill in the art for doses and methods of administration of the radioactive toxic additional therapeutic agent to enable one of skill in the art to practice the present invention.

The well-published literature of ADEPT (which teaches the conversion of a pro-drug to an active drug by the enzyme moiety of a previously bound bispecific reagent) provides a valid working example for the present invention in which the first therapeutic agent is converted to the first extra-cellular precipitate by the enzyme moiety of the previously bound first bispecific reagent. Even in the absence of *in vivo* working examples, the disclosure in the specification of the present invention enables one of skill in the art to predict with high expectation of success, and without undue experimentation, that the first extra-cellular precipitate will form from the first therapeutic agent via the action of the first enzyme moiety of the first bispecific reagent, and that the first extra-cellular precipitate formed from the first therapeutic agent will accumulate in the extra-cellular fluid and will function as described. (For evidence that the insoluble precipitate will be removed by convection and phagocytosis slower from tumor tissue than for normal tissue, and thus one skilled in the art is able to successfully predict that the first therapeutic agent will be retained for an extended period of time in tumor tissue and therefore function as disclosed in the present invention, please see Response 4 below.) Furthermore, Applicant has unpublished *in vitro* data produced by an independent third party (Marin Biologic of Tiburon, California) demonstrating that an immobilized enzyme (beta-galactosidase on beads in either phosphate-buffered saline or 1% agarose) converted the soluble precipitable material 4-chloro-3-indolyl-beta-D-galactopyranoside

(akin to the first therapeutic agent of the present invention) to an insoluble indigo precipitate.

The following sample calculation illustrates how the specification and references for the working example of ADEPT, plus the working example of the 90%-curative treatment of thyroid cancer by the administration and immobilization of radio-iodide, provide sufficient guidance to one of skill in the art for doses and methods of administration of the first bispecific reagent, first therapeutic agent, second bispecific reagent, and radioactive toxic additional therapeutic agent of the present invention:

(1) Re: the current 90%-curative treatment of thyroid cancer with radio-iodide for 10 grams of tumor:

An attempt is made to accumulate 10(4) -- that is, ten thousand -- Iodine-131 atoms per cancer cell. This translates to 3x10(14) isotope atoms per 10 grams of tumor {10 grams X 3x10(9) cells per gram X 10(4) isotope atoms per cell}. The isotopes circulates with a biological half-life of approximately 3-10 hours (10 hours is used for these calculations) and remains in the tumor with a biological half-life of 1-3 days (3 days is used for the calculations). A low test dose of isotope and measuring thyroid uptake and blood levels determines the required therapeutic dose of isotope; there is NO standard uniform therapeutic dose which is used.

(2) Re: the present invention for 10 grams of tumor:

(a) 10 grams of tumor contain 3x10(9) cells.

(b) There are 10(4)-10(5) non-endocytosing receptors per cell {10(5) receptors per cell is used for these calculations}.

(c) Multiplying (a) X (b), there are 3x10(14) non-endocytosing receptors per 10 grams of tumor.

(d) Approximately 1% {10(-2)} of the administered dose of an antibody targeting agent binds to 10 grams of tumor.

(e) Using (c) and (d), 3x10(16) {= 3 x10(14) X 10(2)} (antibody) first targeting agent moiety molecules must be administered to bind one molecule to each non-endocytosing receptor.

(f) Since each first targeting agent moiety molecule has attached to it one non-mammalian first enzyme moiety molecule (forming the first bispecific reagent), there will be 3x10(14) first enzyme moiety molecules bound per 10 grams of tumor after the bispecific reagent has been administered and allowed to bind to the non-endocytosing receptors.

(g) The turnover number of the first enzyme moiety (= rate of enzyme conversion of substrate into product) is approximately 10(2) per second or more.

(h) Since there are approximately 10(5) seconds per day, 3x10(14) first enzyme moiety molecules will convert 3x10(21) first therapeutic agent molecules to first extra-cellular precipitate molecules per day {3x10(14) first enzyme moiety molecules X 10(5) seconds per day X 10(2) per second turnover number of enzyme}. Thus, after administering the first bispecific reagent followed by the first therapeutic agent, there will be 3x10(21) molecules of insoluble non-digestible first extra-cellular precipitate with antigenic epitopes per 10 grams of tumor. {Note that if the first therapeutic agent is radio-labeled as per Claim 83, then 3x10(21) radioactive first extracellular precipitate molecules will be retained per 10 grams of tumor}.

(i) Following the reasoning above, the second bispecific reagent (which consists of a targeting agent moiety specific for one of the antigenic epitopes on the first extra-cellular precipitate plus a non-mammalian second enzyme moiety) is administered in sufficient quantity to bind one molecule of it to each molecule of first extra-cellular precipitate (via the antigenic epitopes on the precipitate).

(j) 3x10(21) second enzyme moiety molecules will convert 3x10(26) molecules of soluble radioactive additional therapeutic agent to the radioactive toxic new form per day

{= approximately 1.5 x10 (26) molecules per 10 hours for comparison to the thyroid cancer treatment model in (1) above}, and the radioactive toxic new form will remain in the extra-cellular fluid of the tumor with a biological half-life of at least 3 days (this is a conservative estimate and is the same as the biological half-life in the thyroid cancer model described above).

Thus the present invention has the potential to deposit and retain 5x10(11) times as many radioactive molecules in the tumor than does the 90%-curative treatment of thyroid cancer with radio-iodide {1.5x10(26) molecules versus 3x10(14) molecules}.

In actual practice, the number of isotope atoms deposited in the present invention is likely to be less than 1.5x10(26) per 10 hours because of a number of factors such as (a) steric hindrance, (b) macrophage uptake and convective flow into lymphatics of the first extra-cellular precipitate and the radioactive toxic new form, (c) endogenous antibody molecules which bind to the cell receptors and therefore compete with the administered first bispecific reagent, (d) complexing of the first targeting agent moiety of the first bispecific reagent with soluble cell receptors in the circulation, such complexes being quickly engulfed by macrophages of the liver, lung and spleen, and (e) loss of bispecific reagent bound to the receptors over time.

However, the huge potential excess of radioactive molecule deposition compared to thyroid cancer treatment (combined with the conservative estimate of the retention time of the radioactive toxic new form in the tumor, and the short duration of time necessary for the isotope to circulate in the blood) should enable the present invention to achieve micro-regional destruction of tumor cells with minimal systemic radioactive toxicity.

See also Mayers declaration.

RESPONSE TO CLAIM REJECTIONS IN SECTION 8 OF PAPER NO. 33, UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 27, SECTION 12, PAGE 10 OF ACTION

In the Amendment mailed on November 27, 2000 and repeated herein, the word "molecule" was deleted from claims 71 and 72. It is submitted that the amendment overcame the rejection.

RESPONSE TO CLAIM REJECTIONS IN SECTION 8 OF PAPER NO. 33 UNDER 35 USC, SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 27, SECTION 13, PAGE 10 OF ACTION

In the Amendment mailed on November 27, 2000 and repeated herein, ". . . reduce the abiity of the indoxyl compounds and the extra-cellular precipitate to . . ." and ". . . by at least one of diffusion and convective flow. . . ." were deleted from claims 77 and 78.

In the Amendment mailed on November 27, 2000 and repeated herein, ". . . by at least one of diffusion and convective flow. . ." was deleted from claim 79.

RESPONSES TO CLAIM REJECTIONS IN SECTION 9 OF PAPER NO. 33, UNDER 35 USC SECTION 112, SECOND PARAGRAPH, BASED UPON PAPER NO. 27, SECTION 14, PAGE 10 OF ACTION

In the Amendment mailed on November 27, 2000, claim 69 was amended to recite, in line 25, delete "a period of time."

Since claim 69 in line 25, recited "for an extended period of time," claim 69 herein has been amended to delete "for an extended period of time".

RESPONSES TO CLAIM REJECTIONS IN SECTION 10 OF PAPER NO. 33,
UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON
PAPER NO. 10, SECTION 8, PAGES 6-18 OF ACTION

Action - Section 8:

Claims 69-83 are rejected under 35 U.S.C. § 102() as being anticipated by WO 91/109134 (see attached abstract).

The claims are drawn to a bispecific reagent having a first enzyme moiety which is a non-mammalian enzyme moiety and a second moiety including a targeting agent which has a substantial affinity for the first target cancer cells and a therapeutic reagent adapted to be converted into an insoluble and non-digestible precipitate by the action of a non-mammalian enzyme.

Response:

The present invention comprises the conversion of a soluble precipitable material (which is not a pro-drug) into an insoluble and non-digestible precipitate by the enzyme moiety of the bispecific reagent. the insoluble precipitate remains adjacent to the bispecific reagent for an extended period of time, such as several days. Thus the precipitate does not enter the systemic body fluids.

The conversion of a soluble precipitable material into an insoluble and non-digestible precipitate is not shown or suggested by International Application Number WO 91/109134 where a soluble agent, being a soluble pro-drug, is converted into a soluble active drug which is digestible and which immediately diffuses away from the bispecific reagent to enter the systemic body fluids.

It is admitted in the Action regarding the reference of International Application Number WO 91/109134, that:

"The reference does not specifically teach that the therapeutic reagents are adapted to be converted into insoluble and non-digestible precipitates."

Therefore claims 69-83 as admitted in the Action can not be rejected under 35 U.S.C. § 102 as being anticipated by the International Application.

The claims to the present invention set forth the characteristics of the precipitate (formed from the soluble therapeutic agent) as being insoluble, non-digestible and having epitopes, one of which is a neo-antigenic epitope.

To the contrary in International Application Number WO 91/109134, the active drug (formed from the soluble pro-drug) is soluble, digestible, and does not have epitopes and does not have a neo-epitope. The active drug (formed from the pro-drug) is not radioactive and is not used to bind any other bispecific reagent.

The claims to the present invention set forth that the epitopes on the precipitate have the intended use of creating a radiation field or of binding a second bispecific reagent, the enzyme moiety of which converts a soluble therapeutic agent into a second precipitate which is radioactive, thereby creating an intense radiation field.

Again to the contrary, in International Application Number WO 91/109134, the active drug (formed from the soluble pro-drug) has the intended use of diffusing through the extra-cellular fluid to have a pharmacological effect (not a radiation effect) on the neighboring cells.

In sum, the therapeutic agent of claims 69-93 is, thus, patentably distinct over the prior art and the product formed from the claimed therapeutic agent is, thus, patently distinct over the prior art.

RESPONSES TO CLAIM REJECTIONS IN SECTION 10 OF PAPER NO. 33, UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 18 (NOT PAPER NO. 15), SECTION 8, PAGES 8-9 OF ACTION

Action -- Paper 18, page 9

> The argument has been noted but has not been found persuasive because of the broadly recited prodrugs in WO 91/109134. Applicant is invited to submit objective evidence to estalish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product, particularly as drawn to the anti-cancer drugs recited on page 9, line 14 through page 1.

Response:

> See Declaration of Dr. Epstein.

RESPONSES TO CLAIM REJECTIONS IN SECTION 10 OF PAPER NO. 33, UNDER 35 USC SECTION 112, FIRST PARAGRAPH, BASED UPON PAPER NO. 27, SECTION 11, PAGE 9 OF ACTION

See responses to claim rejections of Paper No. 10, Section 8, pages 16-18 and Paper No. 15, Section 10, pages 8-9, above.

Section 11 of the Action mailed February 23, 2001 indicates all other objections and rejections recited in Paper No. 27 are withdrawn.

SUMMARY

It is submitted that the formal objections to claims 69-83 have been overcome by the amendments to the claim herein.

It is further submitted that claims 69-83 have been patentably distinguished over the references.

Therefore, it is submitted that claims 69-83 should now be found to be in condition for allowance.

Favorable action is solicited.

Respectfully submitted,

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Dated: August 13, 2001